

REMARKS

In view of the following remarks, the Examiner is requested to withdraw the rejections and allow Claims 28-59 and 61 the only claims pending and currently under examination in this application.

The Examiner is thanked for the personal interview held with the undersigned on March 25, 2008. During the interview, the above amendments were discussed in the context of the cited combination of Anderson with Schleifer A and Schleifer B. Fig. 1B and Col. 9 of Schleifer B were specifically discussed. The Examiner indicated that if language were introduced into the claims which clearly excluded the "1 to 1" flowthrough embodiment assertedly disclosed in Schleifer B, Fig. 1B, that such amendment would appear to overcome these rejections of record. In response, the Applicants have amended the claims to specify that the entire surface of the substrate that has the plurality of locations is contacted with the same fluid. It is believed this amendment specifically addresses the asserted concern with respect to Schleifer B, Fig. 1B. It is believed that above provides a true account of the substance of the personal interview.

Claims 28 and 56 have been amended solely to further clarify that the claims are directed to a method of *in situ* synthesis of polymeric ligands on a surface of a solid support. It is noted that specific support for the introduce term "entire" with respect to surface is found in the specification at page 24, lines 21 to 25. No new matter has been added by way of these amendments. As no new matter has been added by way of these amendments, entry thereof by the Examiner is respectfully requested.

Claim Rejections - 35 USC § 103 Anderson, Schleifer (A), and Schleifer (B)

Claims 28-32, 34-36, 38-44, 46-48, 50, 54-55, and 61 were rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Anderson et al. (U.S. Patent No. 5,186,824), in view of Schleifer (A) (U.S. Patent No. 6,077,674) or Schleifer (B) (U.S. Patent No. 6,309,828).

In maintaining the rejections in the previous office action, the Examiner has

asserted that the claim language still encompass methods in which oligonucleotides are prefabricated and deposited pre-made onto different locations of a substrate.

While not agreeing with the position of the office, the claims have been further amended to clarify that the final array product includes the same substrate on which the oligonucleotides are produced, by specifying the same surface throughout the claims. As such, it is believed that the rejection may be withdrawn and that all of the claims are allowable.

It is submitted that the wording of the claims makes the claims directed to an *in situ* fabrication process in which an addressable array is produced by synthesizing polymeric ligands directly on the surface of a solid support in manner that sequentially adds the monomeric units one at time.

Anderson does not teach or suggest the *in situ* production of an addressable array of oligonucleotides. Nor does the Examiner allege that Anderson teaches or suggests an *in situ* process. Accordingly, Anderson is fundamentally deficient in failing to teach or suggest an *in situ* fabrication process as claimed.

Since Schleifer (A) was cited by the Examiner solely for the purpose of an alleged teaching of making an addressable array by depositing pre-made polymers onto a surface of a support, it fails to make up for the fundamental deficiencies in Anderson. In fact, because Schleifer (A) only teaches one to deposit pre-made polymers onto a surface, they teach away from producing the polymers on the surface *in situ*.

In attempting to establish the rejection, the Examiner further asserts that Schleifer (B) "teaches an embodiment wherein *in situ* synthesis methods are performed to produce an addressable array." The Examiner cites column 10, lines 30-35 to support this assertion. However, this passage is directed to a synthesis unit illustrated in Fig. 1B, where there is a bead in each of plurality of synthesis chambers. It is noted that the claims explicitly distinguish over any teaching provided in Schleifer B, Fig. 1B, by specifying that the entire surface of the substrate is contacted with the fluid, not just individual synthesis chamber.

Even if one were to construe as the whole synthesis unit of Schleifer (B) containing beads as one substrate comprising a plurality of addressable features, as recited in the rejected claims, the combination of Schleifer (B) with Anderson would not render the claimed invention obvious for the reasons set forth below.

In making this rejection, the Examiner asserts that Schleifer (B)'s teaching of fabricating "an addressable array" in combination with Anderson's teaching of fluid displacement renders the claims obvious. The Applicants submit that if the Examiner were to modify Schleifer (B) along with Anderson to read onto the Applicants' claimed invention, the proposed combination would either change the principle of operation of the methods taught by the references or render them inoperable. Under current law, such logic cannot be used to establish a *prima facie* case of obviousness.

It is well established that a reference cannot render an invention obvious

if the proposed modification or combination of the prior art would change the principle of operation of the prior art invention being modified...¹

or

if proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose.²

As noted above, Schleifer (B) assertedly teaches *in situ* fabrication on a bead located in individual synthesis chambers in a synthesis unit. Anderson teaches an enclosed rotor that permits separations involving phases of different density. In Fig. 1 and 2A-2D pointed out by the Examiner in Anderson, solid phase reactions performed on solid support such as CPG are retained in suspension inside Anderson's rotor during fluid displacement. If one were to combine the teachings of Schleifer (B) and that of Anderson's, one would end up having Schleifer's synthesis unit inside the enclosed rotor. Since a glass bead is not an addressable array nor can Schleifer's synthesis unit exist in suspension, it would render either Schleifer's method or Anderson's method inoperable.

This combination would also render Schleifer's method inoperable for the following reason. As the Examiner points out in Schleifer (B)'s column 10, different "sets of nucleic acid molecules are deposited using contact-printing on the substrate." Such contact printing to specific addresses on an array substrate would be inoperable if the substrate were to be enclosed in Anderson's rotor.

¹ *In re Ratti*, 270 F.2d 810, 123 USPQ 349 (CCPA 1959); MPEP 2143.01 VI

² *In re Gordon*, 733 F.2d 900, 221 USPQ 1125 (Fed. Cir. 1984); MPEP 2143.01 V

Furthermore, if one were to modify the teachings of Schleifer (B) or Anderson to comport with the Applicants' claimed invention, the proposed modification would change the principle of operation of the cited references. An operable modification would not contain the element of fluid displacement in a rotor or column taught by Anderson since it would be inoperable as described above. A *prima facie* case of obviousness cannot be established by completely eliminating the principle operation of Anderson.

In addition to the incompatibility of the principle of operation discussed above, the Examiner has not articulated any reasoning why one of skilled in the art would combine Anderson with Schleifer (B). The Examiner asserts that one of ordinary skilled in the art would want to combine the references to remove unwanted reagents from nucleic acid reaction. However, microcapillary **11** (column 10, line 16) in Schleifer (B) provides the draining of reagents from the synthesis unit. There is no reason to use a fluid displacement in a rotor simply to remove fluids in Schleifer (B)'s synthesis unit, when the methods are incompatible.

In view of the foregoing discussion, the combination of Schleifer (B) and Anderson cannot render the rejected claims obvious because the proposed modification would either change the principle of operation or render the methods taught inoperable. Moreover, there is no apparent reason to modify the references in the manner suggested by the Examiner aside from the hindsight provided by the instant application. As such, the combination of these cited references cannot be used to establish a *prima facie* case of obviousness. Thus, the Applicants request that the rejection be withdrawn.

As such, Claims 28-32, 34-36, 38-44, 46-48, 50, 54-55 and 61 are not obvious under 35 U.S.C. § 103(a) over the cited combination of Anderson, in view of Schleifer (A) or Schleifer (B). Therefore, the Applicants respectfully request that this rejection be withdrawn.

Claim Rejections - 35 USC § 103 Anderson and Schleifer (B)

Claims 33, 51, 52 and 56-59 were rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Anderson et al. (U.S. Patent No. 5,186,824), in view of Schleifer (B) (U.S. Patent No. 6,309,828). The Applicants traverse this rejection.

As noted above, a *prima facie* case of obviousness may not be supported by a combination of references that would render their original operation inoperable or change their principle of operation. It also requires an articulated reasoning why one of skilled in the art would combine the cited references in the manner suggested by the Examiner.

Claims 33, 51, 52 and 56-59 ultimately depends on Claim 56, which contains the limitations of “an addressable array comprising a substrate of at least two oligonucleotides bonded to different locations on a surface of the substrate” and “displacing the deblocking fluid from the surface.”

It seems that the Examiner repeats the same argument for this rejection as that for the previous rejection. The Examiner alleges that it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to apply the displacement fluid synthesis steps of Anderson to the polymer synthesis of Schleifer (B).

In making this rejection, the Examiner asserts that Anderson teaches a method for producing a substrate with at least two oligonucleotides bonded to different locations on a surface of the substrate by citing column 19, lines 55-58. However, a detailed analysis of the cited passage reveals that Anderson is synthesizing polymer on a bead. There is no teaching or suggestion that the bead is an addressable array with at least two different oligonucleotides. There is also no teaching or suggestion that any substrate used in Anderson is an addressable array.

The Examiner reiterates that one of skilled in the art would have reason to combine Anderson and Schleifer (B) to remove unwanted reagents. However, as discussed above, Schleifer (B) provides a microcapillary to remove unwanted reagents. Moreover, as discussed previously, in view of the inoperability and the incompatibility of combining *in situ* synthesis of an addressable array with fluid displacement in Anderson's rotor, this combination cannot support a *prima facie* case of obviousness.

As such, the combination of Anderson and Schleifer (B) in the manner suggested by the Examiner is impermissible. Further, the Examiner has not articulated any reasoning why one of skilled in the art would combine the cited references. Accordingly, this rejection may be withdrawn.

Claim Rejections - 35 USC § 103 Anderson, Schleifer (A), Schleifer (B), and Greene

Claim 37 was rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Anderson et al. (U.S. Patent No. 5,186,824), in view of Schleifer (A) (U.S. Patent No. 6,077,674) or Schleifer (B) (U.S. Patent No. 6,309,828), and further in view of Greene et al. (*Protective Groups in Organic Synthesis*, 3rd ed., Wiley and Sons, New York, 1999, page 106).

As discussed above, Anderson, Schleifer (A), and Schleifer (B) cannot be combined to support a *prima facie* case of obviousness because at least one method would be rendered inoperable. Moreover, there is no apparent reason to combine the references in the manner suggested by the Examiner aside from the hindsight provided in the instant application.

Greene is cited solely for its alleged disclosure that the purging fluid density is higher than the deblocking fluid density. As such, Greene fails to remedy the deficiencies discussed above. Accordingly, Claim 37 is not obvious over the cited combination of Anderson, in view of Schleifer (A) or Schleifer (B), and further in view of Greene, and the Applicants respectfully request that the rejection be withdrawn.

Claim Rejections - 35 USC § 103 Anderson, Schleifer (A), Schleifer (B), and Mian

Claim 45 was rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Anderson et al. (U.S. Patent No. 5,186,824), in view of Schleifer (A) (U.S. Patent No. 6,077,674) or Schleifer (B) (U.S. Patent No. 6,309,828), and further in view of Mian et al. (U.S. Patent No. 6,319,469).

As reviewed previously, Anderson, Schleifer (A), and Schleifer (B) cannot be combined to support a *prima facie* case of obviousness because at least one method would be rendered inoperable. Moreover, there is no apparent reason to combine the references in the manner suggested by the Examiner aside from the hindsight provided in the instant application.

Mian is solely cited for its alleged disclosure of flow rate of purging fluid and as such, cannot remedy the deficiencies of Anderson, Schleifer (A), and Schleifer (B). Accordingly, Claim 45 is not obvious over the cited combination of Anderson, in

view of Schleifer (A) or Schleifer (B), and further in view of Mian, and the Applicants respectfully request that the rejection be withdrawn.

Claim Rejections - 35 USC § 103 Anderson, Schleifer (A), Schleifer (B), and Gamble

Claim 49 was rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Anderson et al. (U.S. Patent No. 5,186,824), in view of Schleifer (A) (U.S. Patent No. 6,077,674) or Schleifer (B) (U.S. Patent No. 6,309,828), and further in view of Gamble et al. (U.S. Patent No. 5,874,554).

As explained above, Anderson, Schleifer (A), and Schleifer (B) cannot be combined to support a *prima facie* case of obviousness because at least one method would be rendered inoperable. Moreover, there is no apparent reason to combine the references in the manner suggested by the Examiner aside from the hindsight provided in the instant application.

As Gamble was cited solely for this disclosure of pulse-jet deposition, Gamble fails to make up the deficiencies discussed above. Accordingly, Claim 49 is not obvious over the cited combination of Anderson, in view of Schleifer (A) or Schleifer (B), and further in view of Gamble, and the Applicants respectfully request that the rejection be withdrawn.

Claim Rejections - 35 USC § 103 Anderson, Schleifer (A), Schleifer (B), and Farr

Claim 53 was rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Anderson et al. (U.S. Patent No. 5,186,824), in view of Schleifer (A) (U.S. Patent No. 6,077,674) or Schleifer (B) (U.S. Patent No. 6,309,828), and further in view of Farr (U.S. Patent No. 3,969,250).

As explained above, Anderson, Schleifer (A), and Schleifer (B) cannot be combined to support a *prima facie* case of obviousness. As Farr was cited solely for the asserted teaching of the stratification of liquids using a pressure gradient, Farr fails make up for the above deficiencies. As such, Claim 53 is not obvious over Anderson, in view of Schleifer (A) or Schleifer (B), and further in view of Farr, and this rejection may be withdrawn.

CONCLUSION

In view of the amendments and remarks above, the Applicants respectfully submit that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, please telephone Bret Field at (650) 327-3400.

The Commissioner is hereby authorized to charge any fees under 37 C.F.R. §§ 1.16 and 1.17 which may be required by this paper, or to credit any overpayment, to Deposit Account No. 50-1078.

Respectfully submitted,

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By: /Bret E. Field, Reg. No. 37,620 /
Bret E. Field
Registration No. 37,620

AGILENT TECHNOLOGIES, INC.
Legal Department, DL429
Intellectual Property Administration
P.O. Box 7599
Loveland, CO 80537-0599

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